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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/080,713	02/25/2002	Alan Colman	10758.105015CON	9155

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EXAMINER	
TON, THAIAN N	

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1632	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/080,713	COLMAN ET AL.	
	Examiner	Art Unit	
	Thaian N. Ton	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *24 June 2010*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *See Continuation Sheet* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *62,63,65,66,73,75-79,82,87-90,99,100,102-110,113,118-125,131 and 133-152* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

Continuation of Disposition of Claims: Claims pending in the application are 62,63,65,66,73,75-79,82,87-90,99,100,102-110,113,118-125,131 and 133-152.

DETAILED ACTION

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 6/24/10 has been entered.

Applicants' Amendment and Response, filed 6/24/10, has been entered. Claims 62, 65, 66, 73, 82, 90, 99, 100, 113, 121, 122, 131, 133 are amended; claims 70-72 are cancelled; claims 134-152 are newly added; claims 62, 63, 65, 66, 73, 75-79, 82, 87-90, 99, 100, 102-110, 113, 118-125, 131, 133-152 are pending and under current examination.

Double Patenting

The prior rejection of claims 62, 63, 65, 66, 70-73, 75-79, 82, 87-90, 99, 100, 102-110, 113, 118-125, 131, 133 as being provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 62-69, 71-75, 78-86, 88-92, 95-97 of copending Application No. 11/641,644 is rendered moot in view of the abandonment of the '644 case.

Claim Objections

Claim 146 is objected to because of the following informalities: the claim recites "wherein the endogenous regulatory comprises" in line 1. This claim is grammatically incorrect, and appears that this phrase should read "wherein the endogenous regulatory *region* comprises." Appropriate correction is required.

Enablement

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 62, 63, 65, 66, 73, 75-79, 82, 87-90, 99, 100, 102-110, 113, 118-125, 131, 133-152 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for:

Methods of producing a non-primate transgenic mammal, the method comprising:

(a) modifying the nuclear genome of a fibroblast cell that has a sufficient lifespan to be useful for genetic modification, wherein the genome has a normal karyotype, at an endogenous locus by homologous recombination;

(b) transferring the modified nuclear genome of the fibroblast cell to an oocyte, two cell embryo or zygote all of which have been enucleated which is capable of producing a viable nuclear transfer unit;

(c) activating the nuclear transfer unit thereby producing an embryo;

(d) transferring the embryo to a final surrogate mother which is a suitable host for the mammal to be grown to term; and

(e) allowing the embryo to develop to term, thereby producing a non-primate transgenic mammal.

The specification does not reasonably provide enablement for 1) genetically modifying a specific endogenous locus of a fibroblast cells using techniques other than homologous recombination; 2) producing transgenic humans. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

Enablement is considered in view of the Wands factors (MPEP 2164.01(A)). These include: nature of the invention, breadth of the claims, guidance of the specification, the existence of working examples, state of the art, predictability of

the art and the amount of experimentation necessary. All of the Wands factors have been considered with regard to the instant claims, with the most relevant factors discussed below.

Nature of the Invention. The claimed invention is directed to methods of producing non-human transgenic mammals and transgenic mammals by genetically modifying the nuclear genome of a fibroblast cell, utilizing the fibroblast cell as a donor cell in nuclear transfer (NT) techniques to produce an NT embryo, and allowing the NT embryo to develop to term to produce either a non-human transgenic animal, or a transgenic animal, respectively.

Breadth of the claims. The breadth of the claims encompasses modifying a specific locus of the fibroblast genome utilizing techniques other than homologous recombination; and the production of transgenic primates by nuclear transfer.

Guidance of the Specification/The Existence of Working Examples. The instant specification contemplates a broad list of suitable somatic cells that would be used in the claimed methods [see p. 5, lines 21-30], and discusses the current limitations in gene targeting in somatic cells; particularly, that homologous recombination in somatic cells is an infrequent event and that it is often necessary to transfect and screen large populations of cells in order to pick a specific clone and that somatic cells have a limited lifespan in culture. See pp. 21-22. The specification teaches that somatic cells that have been shown to support NT are usually of fibroblast origin, although NT has been shown to be successful in cumulus, oviduct and mammary oviduct and granulosa cells. See p. 27, lines 5-8. The working examples of the specification are directed to gene targeting and subsequent NT of primary ovine fetal fibroblasts [Examples 1-4], gene targeting of primary mammary epithelial cells [Example 5] and the gene targeting of porcine fetal fibroblasts [Example 6], gene targeting in primary bovine fetal fibroblasts [Example 7].

State of the Art/Predictability of the Art.

1. *Techniques for Gene Targeted Modifications.* The claims are directed to the production of a transgenic mammal. Specific embodiments are directed to specific types of gene targeting, including upregulation, replacement, or inactivation of a gene (see claims 65-66, for example). Further embodiments are directed to placing a marker gene at an endogenous locus (claims 75-79, for example); or to place a transgene adjacent to an endogenous promoter in the nuclear genome (claims 102+). The as-filed disclosure teaches that the claimed methods are used to produce cells with specific genetic modifications produced by gene targeting (Abstract). The specification teaches that the methods of the invention allow for placing a transgene at a predetermined site (¶23, published Application); and preferably the gene targeting event occurs by homologous recombination (¶33). Thus, the claims as a whole require homologous recombination in order to introduce a specific genetic modification into the genome of a fibroblast. The claims as amended no longer recite that the modification is produced by homologous recombination. The as-filed disclosure does not provide any other means in order to specifically target a specific endogenous locus in a fibroblast's genome in a predictable manner, other than using homologous recombination. Additionally, Clark *et al.* (**Nature Reviews**: 4: 825-833, 2003) reviews the state of the art of transgenic livestock, state that, "Pro-nuclear injection enables only the random addition of genes to the germline. It does not allow the precise modification of the germline that is required for the specific deletion or modification of endogenous genes. A high proportion of transgenic lines that pro-nuclear injection generates do not efficiently express transgenes because of silencing effects at the site of integration." See p. 827, col. 3 Gene Targeting. Additionally, the Examiner notes that Capecchi (**Scientific American**, 270(3): 34-41, 1994, cited previously) teaches that at the time of filing, would understand that a knockout or a knock in of a gene is accomplished by homologous recombination. Capecchi teaches how targeted gene replacement is accomplished in cultured cells (p. 36, Figure 1). Accordingly, in view

of the teachings of the art, which support the pronuclear microinjection results in random integration of a transgene into a cell's genome, and the lack of guidance provided by the specification with regard to any other means to produce a gene-targeted fibroblast which can then be used for nuclear transfer, the claims have been limited to production of gene-targeted fibroblasts by homologous recombination.

2. *Production of Transgenic Primates.* Claims 133 and its dependent claims recite methods for producing transgenic offspring, which encompasses production of transgenic primates. However, these embodiments are not enabling because of the art-recognized inability to clone primates. Vogel (**Science**, 300:225 and 227, 2003) state that Rhesus monkey NT-generated embryos seemed normal at their early stages but were unable to develop further when implanted into a surrogate mother. This was because the cells had the wrong number of chromosomes, and that this aneuploidy resulted in the abortion of the fetus. This was found to also be the case with human NT embryos. See p. 225. Simerly *et al.* (**Science**, 300:297, 2003) state that, "Primate NT appears to be challenged by stricter molecular requirements than in other animals ... With current approaches, NT to produce embryonic stem cells in nonhuman primates may prove difficult – and reproductive cloning unachievable." See p. 297, 3rd column, last sentence. Additionally, Simerly *et al.* (**Dev. Biol**, 276: 237-252, 2004) teaches that, "As previously reported in NHPs, few SCNT embryos (<1%) developed to blastocyst stage. Here, despite SCNT embryos appearing morphologically normal, many NT constructs generated by aspirated enucleation still demonstrate anueploidy. DNA missegregation is already prevalent by first mitotic telophase, as evident by lagging chromosomes and loosely organized DNA at the spindle poles ... As development proceeds to the 8-cell stage, monastral interphase microtubule patterns either lacing DNA or with inappropriate chromosomes are observed." See p. 242, col. 1, 2nd full ¶ and Figure 2. Simerly teaches that:

> "Taken together, the data suggest that meiotic spindle removal depletes the egg cytoplasm of HSET, a vital protein for first mitotic spindle pole formation. Also the residual NuMA, retained within the oocyte's cytoplasm following spindle extrusion and imported into the interphase nucleus following SCNT, is not effectively targeted to the spindle poles in mitotic constructs or is below threshold concentrations, perhaps indicating interference with mechanisms that recruits NuMA to the microtubule minus-ends (Compton, 1998)." See p. 248, col. 1, 1st ¶.

Mitalipov (Methods in Mol. Bio, 348: 151-168, 2006) is post-filing art that reviews the state of the art of primate nuclear transfer. They state that, "We were initially successful in producing monkeys by NT using embryonic blastomeres as the source of donor nuclei and have repeated that success. However, when somatic cells are used as nuclear donor cells, the developmental potential of monkey SCNT embryos is limited, and somatic cell cloning has not yet been accomplished in primates." See p. 151, Summary). They further state that, "Remarkable progress in mammalian cloning has been achieved in the past several years. However, somatic cell cloning has not yet been accomplished in primates ...."The developmental potential of SCNT monkey embryos has been limited, seldom progressing beyond the eight-cell stage in vitro." See p. 152, paragraphs 2-3.

The Amount of Experimentation Necessary. Accordingly, in view of the lack of teachings or guidance, provided by the specification, with regard to utilizing any other means, other than homologous recombination, to modify the nuclear genome of a fibroblast cell at an endogenous locus; the lack of teachings or guidance with regard to the production of cloned primate animals, the state of the art, which teaches that pronuclear injection results in random integration of the transgene in transgenic animals, the state of the art, which shows that cloning of primates is undeveloped and unpredictable, it would have required the skilled artisan to practice undue experimentation to make and/or use the claimed invention.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 87, 118, 138, 142, 143 and 146 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 87 and 118 are unclear. The metes and bounds of these claim cannot be determined because the claims recite that the cell is an "epithelial cell, a fibroblast cell, an endothelial cell, or a muscle cell." Claim 87 depends from claim 62 and claim 118 depends from claim 90. It is unclear what "the cell" refers to. Claims 62 and 90 recite a "fibroblast cell." The cells recited in claims 87 and 118, other than a fibroblast cell, are not fibroblast cells. Accordingly, the claims are indefinite.

Claim 138 recites that the multiple genetic modifications occur "subsequently". It is unclear what "subsequently" refers to, as it is a relative term.

Claim 142 recites the limitation "the fetus" in line 1. There is insufficient antecedent basis for this limitation in the claim.

Claim 143 recites the limitation "the adult" in line 1. There is insufficient antecedent basis for this limitation in the claim. The claim is further unclear because it recites that the adult comprises an animal from birth onwards. Claim 143 depends from claim 62, which recites a non-human transgenic mammal. Thus, the term "animal" is broader than "non-human transgenic mammal." The metes and bounds of this claim cannot be determined.

Claim 146 recites the limitation "the polyadenylation site" in lines 1-2. There is insufficient antecedent basis for this limitation in the claim.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

The changes made to 35 U.S.C. 102(e) by the American Inventors Protection Act of 1999 (AIPA) and the Intellectual Property and High Technology Technical Amendments Act of 2002 do not apply when the reference is a U.S. patent resulting directly or indirectly from an international application filed before November 29, 2000. Therefore, the prior art date of the reference is determined under 35 U.S.C. 102(e) prior to the amendment by the AIPA (pre-AIPA 35 U.S.C. 102(e)).

Claims 62, 63, 65, 66, 75, 76, 82, 87-90, 99, 100, 106, 113, 118, 119, 120-122, 131, 133 and newly added claims 134-136, 140, 149-152 stand rejected under 35 U.S.C. 102(b) as anticipated by Campbell *et al.* (WO 97/07669, published 6 March 1997, Applicants' IDS).

Applicants' Arguments. Applicants argue that Campbell is non-enabled, and that the non-enablement of Campbell does not dictate the non-enablement of the claimed invention. Applicants argue that Campbell was the first to produce a viable animal using SCNT, but this is not Applicants' invention. Rather, Applicants' invention is a method of producing a viable animal using SCNT, where the somatic cells have been genetically modified. Applicants argue that Campbell and others spoke of the desirability of Applicants' invention, but there is an important difference between describing the desirability of a given invention or even speculating about how one of skill in the art might approach the inventive task and actually providing a disclosure sufficient to permit one of skill in the art to make

and use that inventions. Applicants argue that Campbell did not provide a disclosure sufficient to permit one of skill in the art to make and use the claimed invention, and therefore is non-enabled. Applicants argue that the *Nature* article stated that no one had been able to produce a viable animal using genetically modified somatic cells in NT. Applicants argue that the Examiner has not responded to Applicants' arguments regarding the non-enablement of Campbell other than to state that Campbell teaches exactly what is claimed. See page 9 of the Response.

Response to Arguments. These arguments have been considered, but are not persuasive. Preliminarily, the Examiner asserts that all of Applicants' arguments have been thoroughly responded to in prior Office actions. In particular, with regard to Campbell's asserted lack of enablement, the Examiner argues that Campbell teaches the exact method steps that are instantly claimed. That is, Campbell teach methods of modifying the exact same cell type (a fibroblast), to produce the same result (a non-human transgenic animal). If Applicant feels the art is not enabling, and the claims cannot be distinguished from the art, then Applicant's claims must also lack enablement. It is up to Applicant to amend the claims to be enabled and distinguish from the art. However, the effect is inherent in the art applied, as the case law states if an invention and the art have the same structure all properties of one will be found in the other. Applicant is encouraged to amend the claims to overcome the art. See also, MPEP ¶2121.01 which states in part that, "A reference contains an "enabling disclosure" if the public was in possession of the claimed invention before the date of invention. "Such possession is effected if one of ordinary skill in the art could have combined the publication's description of the invention with his [or her] own knowledge to make the claimed invention." *In re Donohue*, 766 F.2d 531, 226 USPQ 619 (Fed. Cir. 1985)."

In the instant case, because the method steps taught by Campbell recite the same method steps as the instant invention, the result must be inherent in the

method. Applicants have not provided any guidance to show how Campbell's techniques would not result in a non-human transgenic mammal. Applicants have not distinguished how the instant invention differs from Campbell's invention such that Campbell's methods are non-enabling.

See also, MPEP §2121 (1) When the reference relied on expressly anticipates or makes obvious all of the elements of the claimed invention, the reference is presumed to be operable. Once such a reference is found, the burden is on applicant to provide facts rebutting the presumption of operability. *In re Sasse*, 629 F.2d 675, 207 USPQ 107 (CCPA 1980). See also MPEP § 716.07.

Further MPEP §2121(2) states that: A prior art reference provides an enabling disclosure and thus anticipates a claimed invention if the reference describes the claimed invention in sufficient detail to enable a person of ordinary skill in the art to carry out the claimed invention; "proof of efficacy is not required for a prior art reference to be enabling for purposes of anticipation." *Impax Labs. Inc. v. Aventis Pharm.Inc.,* 468 F.3d 1366, 1383, 81 USPQ2d 1001, 1013 (Fed. Cir. 2006). See also MPEP § 2122.<

Thus, the MPEP makes clear that if 1) the prior art expressly anticipates all the elements of the claimed invention, it is operable; and 2) proof of efficacy is not required for a prior art reference to be enabling. In the instant case, because Campbell teaches each and every method step required by the claims, it must be enabled, absent specific evidence to the contrary. Finally, the proof of efficacy is not required for Campbell to be enabling for the purposes of anticipation. Thus, Applicants have not met the burden as to how the instant invention is distinguished from Campbell's methods, such that it would be clear that Campbell's methods are not enabled.

Applicants' Arguments. Applicants argue that the Examiner has not made an enablement rejection; rather the Examiner's suggestion that the claimed invention is in response to the Applicants' statement that Campbell is non-enabled.

Applicants submit that consistent with the Wands factors, a later-filed disclosure can enable a claimed invention even if the same disclosure – early filed – would have not. Applicants argue that several considerations under Wands that differ between Campbell and the claimed invention include 1) the state of the prior art; 2) the amount of guidance provided by the invention (*i.e.*, that the present invention is not the same disclosure); 3) the presence of a working example. Applicants argue that because enablement is determined by reference to Wands, and because the two applications differ with respect to the Wands factors, Applicants submit that Campbell is not enabled. Applicants argue that there is no pending enablement rejection, and that the fact that the present rejection is not formally an enablement rejection should not be a reason to permit conclusory statements relating to enablement of the claimed invention that operate to discourage Applicants from arguing the enablement-based limitations of the prior art and/or to force additional claim amendments, particularly where prior enablement rejections would have been overcome. Applicants argue that they should not have to "pick their poison", and that the claimed invention is enabled, whereas the prior art is no. See p. 10-11 of the Response.

Response to Arguments. These arguments have been considered but are not persuasive. Campbell teaches the same method steps as that which is instantly claimed. Thus, the ordinarily skilled artisan, following Campbell at the time of filing, would have been able to achieve the invention as claimed. The MPEP at §2138.05(a) clearly shows that reduction to practice does not require the disclosure to produce a particular product, but to provide a method of doing so: "Reduction to practice may be an actual reduction or a constructive reduction to practice which occurs when a patent application on the claimed invention is filed. The filing of a patent application serves as conception and constructive reduction to practice of the subject matter described in the application. Thus the inventor need not provide evidence of either conception or actual reduction to practice when relying on the

content of the patent application. *Hyatt v. Boone*, 146 F.3d 1348, 1352, 47 USPQ2d 1128, 1130 (Fed. Cir. 1998)." Because there are no differences between the steps that are disclosed by Campbell and the claimed method, Campbell's method is enabled. If Applicants are asserting that Campbell's methods are not enabled, there must be a distinction between the claimed invention and Campbell's method. This distinction is what is required in the instant claims. Because such an amendment has not been made, the claimed method is the same as that disclosed by Campbell, and therefore, Campbell anticipates the claimed invention.

While the state of the art has bearing on enablement, Applicants have not stated the new development in the area of endeavor, nor as Applicants pointed to the specification wherein such a new development can be found. From Applicants' Response, the reason the present claims are enabled whereas Campbell's disclosure is not cannot be discerned. Furthermore, Applicants, by stating new developments, are arguing limitations that are not found in the claims, and thus, do not apply. Until Applicants provide specific guidance and a detailed account of specific developments that render Campbell's disclosure as non-enabled, the rejection is maintained.

Rejection

Campbell teach methods of producing transgenic animals via nuclear transfer (see Abstract). They teach methods of nuclear transfer, to introduce quiescent cells arrested at G0 into enucleated oocytes (p. 9, lines 1-3 and lines 29-31) and the fusion and activation of the resultant NT unit (page 13), the activation of the resultant cell (p. 14), and then the transferring of the embryo to a surrogate mother in order to develop the embryo to term (p. 15, lines 11-19; p. 18, lines 21-33; p. 20, lines 1-23). They teach that transgenic animals that can be produced by their methods pertain to animals wherein an endogenous gene has been, "deleted, duplicated, activated or modified ..." (p. 6, lines 29-34). They additionally suggest that these modified cell populations include gene additions, gene knockouts, gene

knock ins and other gene modifications, and optionally the cells may be transfected with suitable constructs and with or without selectable markers (p. 20, lines 10-12). They teach that their methods can be used in to produce any animal (p. 5, lines 10+). They teach that the animal can be bred (p. 17, lines 15-19). They teach that the donor nucleus may contain one or more transgenes, and that this genetic modification may be introduced by methods such as electroporation, or lipofectin (p. 7, lines 1-11). They teach that the donor cell can be any somatic cell of normal karyotype, including fibroblasts (p. 7, lines 13+). They teach that the cells are quiescent and in G0 state (p. 8, lines 13-22). They teach serum starvation to produce the G0 cells (p. 8, lines 25-29).

Campbell teaches that the donor nucleus is genetically modified, and that this nucleus may contain one or more transgenes (p. 7, lines 1-5).

Claims 62, 63, 65, 66, 75, 82, 87-90, 99, 100, 106, 113, 118-122, 131, 133 and newly added claims 134-136, 140, 149-152 stand rejected under 35 U.S.C. 102(e) as being anticipated by US Pat. No. 6,147,276 (Issued November 14, 2006, filed February 19, 1997).

Applicants provide no substantive arguments regarding this rejection, therefore this rejection is maintained.

Rejection

Regarding claims 62, 90, 131, 133, 149-152 the '276 patent teaches methods of nuclear transfer to produce transgenic mammals (Abstract). The '276 patent teaches that donor cells can be fibroblasts (col. 4, lines 10-11). The '276 patent teaches producing cloned animals by transferring the donor cell nucleus into an enucleated metaphase II oocyte (col. 5, lines 58+), the activation of the resultant NT unit (col. 6, lines 63+) and developing a cloned animal from the embryo (col. 7, lines 35-44). The '276 patent teaches that transgenic animals can be produced by the claimed methods (col. 3, lines 16-20). The '276 patent teaches specific methods of

modifying endogenous genes, including deletion of specific endogenous genes. These methods require specific targeting, which is only accomplished by homologous recombination.

Regarding claim 63, the '276 patent teaches producing sheep, goat, camels, pigs (col. 3, lines 6-9).

Regarding claims 65, 66, 99, 100, 136 the '276 patent teaches that endogenous genes can be deleted, duplicated, activated or modified (col. 3, lines 43-54 and col. 10, lines 43-49).

Regarding claims 75, 76, 106 the '276 patent teaches that transgenesis may be employed with selectable markers (col. 10, lines 47-49).

Regarding claims 82, 113, the '276 patent teaches that the genetic modification can be produced by lipofection (col. 4, lines 63-64).

Regarding claims 87, 118, the '276 patent teaches utilizing fibroblasts as donor cells (col. 4, lines 10-11).

Regarding claims 88, 89, 119, 120, the '276 document teaches inducing quiescence and arrest the cells in G0 phase of the cell cycle by serum starvation (col. 9, lines 39-41; col. 10, lines 17-18).

Regarding claims 121, 122, the '276 document teaches transfection by electroporation (col. 3, lines 60-64).

Regarding claims 134 and 140,the '276 document teaches that the transgenic donor nucleus may contain one or more transgenes (col. 4, lines 55+).

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be

patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 62, 63, 65, 66, 75-79, 82, 87-90, 99, 100, 106-110, 113, 118-124, 131, 133, 149-152 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Campbell in view of d'Apice *et al.* (**U.S. Pat. No.** 5,849,991 published December 15, 1998).

Applicants' Arguments. Applicants argue that Campbell fails as a reference under §103 for the same reasons as it fails under §102, because it is non-enabled.

Response to Arguments. These arguments have been fully addressed above; the rejection is maintained.

Rejection

Campbell teach methods of producing transgenic animals via nuclear transfer (see Abstract). They teach methods of nuclear transfer, to introduce quiescent cells arrested at G0 into enucleated oocytes (p. 9, lines 1-3 and lines 29-31) and the fusion and activation of the resultant NT unit (page 13), the activation of the resultant cell (p. 14), and then the transferring of the embryo to a surrogate mother in order to develop the embryo to term (p. 15, lines 11-19; p. 18, lines 21-33; p. 20, lines 1-23). They teach that transgenic animals that can be produced by their methods pertain to animals wherein an endogenous gene has been, "deleted, duplicated, activated or modified ..." (p. 6, lines 29-34). They additionally suggest that these modified cell populations include gene additions, gene knockouts, gene knock ins and other gene modifications, and optionally the cells may be transfected with suitable constructs and with or without selectable markers (p. 20, lines 10-12). They teach that their methods can be used in to produce any animal (p. 5, lines 10+). They teach that the animal can be bred (p. 17, lines 15-19). They teach that the donor nucleus may contain one or more transgenes, and that this genetic modification may be introduced by methods such as electroporation, or lipofectin (p. 7, lines 1-11). They teach that the donor cell can be any somatic cell of normal

karyotype, including fibroblasts (p. 7, lines 13+). They teach that the cells are quiescent and in G0 state (p. 8, lines 13-22). They teach serum starvation to produce the G0 cells (p. 8, lines 25-29).

Although Campbell do not specifically teach knockout of the alpha 1-3 galactosyltransferase gene, prior to the time of the claimed invention, d'Apice teach methods for reduction or elimination of the hyperacute rejection response in human, in particular, by producing knockout animals which lack or have reduced alpha 1-3 galactosyltransferase activity (see col., 1, Field of Invention). They specifically teach the porcine sequence (Figure 4), but teach that variations of these sequences can readily be generated by the skilled artisan (col. 2-3, bridging ¶). They teach generation of mammals lacking alpha 1-3 galactosyltransferase (col. 4, lines 54-60), wherein both copies of the gene are inactivated (col. 5, lines 1-2). d'Apice further teach that their targeting construct can contain a selectable marker, including the gene imparting resistance to the antibiotic G418 (col. 13, lines 20-22). They teach any marker that is suitable for inclusion in a knockout marker can be used (col. 13, lines 26-27). They specifically teach that GFP can be used in a construct, in order to detect gene targeting events. Col. 59, lines 5-9 and lines 23-33.

Accordingly, in view of the combined teachings of Campbell and d'Apice, it would have been obvious for one of skill in the art to modify the teachings of Campbell, to specifically inactivate the alpha 1-3 galactosyltransferase gene in a somatic cell, and to use this somatic cell in methods of nuclear transfer in order to produce an animal, wherein the alpha 1-3 galactosyltransferase gene has been inactivated, with a reasonable expectation of success. One of ordinary skill in the art would have been sufficiently motivated to make this modification, given Campbell's teachings for increasing efficiency of producing transgenic animals, and further, given d'Apice's teachings for the need in the art to produce animals whose organs can then be used for xenotransplantation, wherein the knockout of the alpha 1-3 galactosyltransferase gene reduces or eliminates the hyperacute rejection

response. Additionally, one of skill in the art would have been motivated to modify the targeting construct used to target a somatic cell, with any of the markers or promoters suggested by d'Apice, and instantly claimed, because these techniques were well within the skill of the ordinary artisan. One of skill in the art would readily recognize utilizing various marker genes in order to select for clones when performing transfection experiments.

Thus, the claimed invention, as a whole, is clearly *prima facie* obvious in the absence of evidence to the contrary.

Claims 62, 63, 65, 66, 70, 73, 75-77, 82, 87-90, 99, 100, 102, 105-108, 113, 118-122, 125, 131, 133, newly added claims 144, 145, 149-152 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Campbell in view of Kucherlapati *et al.* (**WO 94/02602**, published February 3, 1994).

Applicants provide the same arguments with regard to Campbell. These arguments are addressed above; the rejection is maintained.

Rejection

Campbell is described above. Campbell does not specifically teach inactivation of an endogenous immunoglobulin gene. However, prior to the time of the claimed invention, Kuncherlapati teach the production of non-human mammals with inactivated endogenous Ig loci (see Abstract). In particular, Kuncherlapati teach an art-recognized interest in producing xenogeneic human monoclonal antibodies using transgenic animals (p. 2, lines 23-31). They teach methods of knocking out of the endogenous Ig loci and knocking in of human Ig (p. 6, lines 6-12; p. 10, lines 10-12). Kuncherlapati teach knockout of the endogenous Ig in mouse ES cells, they suggest producing any mammalian host using their methods (p. 10, lines 1-2, pages 16-17). Additionally, Kuncherlapati teach that their targeting constructs can contain various marker genes, including those which confer G418 resistance (p.

16, lines 34-36). Kuncherlapati further teach that the targeting construct may include a replication system, including a promoter (p. 18, line 8).

Accordingly, given the combined teachings of Campbell and Kuncherlapati, it would have been obvious for one of ordinary skill in the art to use the technology of Campbell, and inactivate an endogenous Ig gene in a somatic cell, with a reasonable expectation of success. Although Kuncherlapati teach knockout of the endogenous Ig in mouse ES cells, Campbell provides the teachings and suggestion to use a somatic cell, and then use the modified somatic cell in methods of NT to produce transgenic animals. One of ordinary skill in the art would have been sufficiently motivated to knockout an endogenous Ig gene, as supported by Kuncherlapati, who teach that it is an art-recognized goal to produce xenogeneic specific binding proteins, such as human monoclonal antibodies (p. 2, lines 23-32) by production of transgenic animals. Additionally, one of skill in the art would have been motivated to modify the targeting construct used to target a somatic cell, with any of the markers or promoters suggested by Kuncherlapati, because these techniques were well within the skill of the ordinary artisan. One of skill in the art would readily recognize utilizing various marker genes in order to select for clones when performing transfection experiments.

With regard to claim 73, this claim only requires that the promoter directs expression of one gene in fibroblast cells. This does not exclude a promoter that directs expression in all cells, such as a ubiquitously expressed promoter.

Thus, the claimed invention, as a whole, is clearly *prima facie* obvious in the absence of evidence to the contrary.

Claims 62, 63, 65, 66, 70, 75, 76, 82, 87-90, 99, 100, 102, 104, 106, 113, 118-122, 131, 133, and newly added claims 134-136, 144, 145, 147, 149-152 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Campbell in view of US Pat. No. 6,013,857 (Filed June 5, 1995, Issued January 11, 2000).

Applicants provide the same arguments with regard to Campbell. These arguments are addressed above; the rejection is maintained.

Rejection

Campbell is described above. They do not specifically teach placing a transgene adjacent to an endogenous promoter in the nuclear genome, wherein the promoter is a milk promoter. However, prior to the time of the claimed invention, the '857 patent discusses producing transgenic bovines for producing recombinant polypeptides in milk (Abstract). Particularly, they teach using endogenous milk regulation (*i.e.*, promoter) sequences (col. 8-9, bridging ¶).

Accordingly, it would have been obvious for one of ordinary skill in the art, to modify the methods, as taught by Campbell, to place a transgene of interest adjacent to an endogenous promoter, such as a milk promoter, with a reasonable expectation of success. One of ordinary skill would have been motivated to make this modification, in view of the '857 patent which teaches that these methods would be used in order to produce recombinant polypeptides of interest from transgenic bovine species and isolate the recombinant polypeptide from milk (Abstract).ok

Thus, the claimed invention, as a whole, is clearly *prima facie* obvious in the absence of evidence to the contrary.

Claims 62, 63, 65, 66, 75, 76, 82, 87-90, 99, 100, 102, 103, 106, 113, 118-122, 131, 133 and newly added claims 144, 145, 148-152 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Campbell in view of Bedalov (**Journal of Biol. Chem.**, 269(7): 4903-4909, 1994) when taken with Rossert (**The J. of Cell Biol.** 129(5): 1421-1432, 1995).

Campbell is described above. They do not specifically teach placing a transgene adjacent to an endogenous promoter in the nuclear genome wherein the promoter is a collagen gene promoter. However, prior to the time of the claimed

invention, Bedalov discuss a transgene containing the COL1A1 promoter fused to a reporter gene and discuss its expression in a variety of mesenchymal cell types, including fibroblasts, osteoblasts and odontoblasts (see p. 4903, 1st col., 1st ¶). Bedalov teaches that transgenic mice which have ~3.5 kb of COL1A1 upstream promoter have strong expression of the reporter gene in high collagen producing tissues, such as tendon, bone and skin (p. 4903, col. 2, first full ¶). Bedalov teach that the COL1A1 construct, including the COL1A1 promoter confers tissue-specific expression in transgenic animals, with no aberrant expression (see pp. 4908-4909, bridging sentence). Bedalov suggest that making transgenic animals with genome-integrated transgenes would allow for further analysis of endogenous gene expression and would provide a model that is more biologically representative for the interaction of trans-acting factors with the sequences in the promoter (p. 4909, 1st full ¶, last sentence).

Accordingly, it would have been obvious for one of ordinary skill in the art, to utilize the teachings to make a transgenic, gene targeted animal, by nuclear transfer, as taught by Campbell, and specifically target a transgene under the expression of a collagen promoter, such as that taught by Bedalov, with a reasonable expectation of success. One of ordinary skill in the art would have been sufficiently motivated to make this modification in view of Bedalov's teachings, which show an art-recognized need to further analyze the expression of the COL1A1 promoter in transgenic animals, and additionally, in view of Rossert, who teach that the precise sequences responsible for the lineage-specific expression of the collagen promoter have not been defined (p. 1421, col. 2, last bridging ¶). Thus, the claimed invention, as a whole, is clearly *prima facie* obvious in the absence of evidence to the contrary.

Claims 62, 141 are rejected under 35 U.S.C. 103(a) as being unpatentable over Campbell *et al.* (WO 97/07669, published 6 March 1997, Applicants' IDS) when taken with US Pat. No. 7,321,075 B2 (Campbell *et al.*, published January 22, 2008).

Campbell is described above. They do not specifically teach that the cells from the embryo are further used for rounds of NT, wherein additional genetic modifications are introduced prior to further rounds of NT. However, prior to the time of filing of the claimed invention, the '075 patent teaches methods of nuclear transfer to produce transgenic animals, and specifically teach that serial nuclear transfer can be used. In particular, they state, "It may be possible for increased yields of viable embryos to be achieved by means of the present invention by clonal expansion of donors and/or if use is made of the process of serial (nuclear) transfer." See col. 8, lines 4-8 and claim 1. Thus, the '075 patent provides clear guidance for using the cells of the embryos for further rounds of NT. Additionally, the '075 patent teaches the production of transgenic animals by the isolation of diploid donor cells, transgenesis, embryo reconstitution by NT, culturing of the NT embryo to blastocyst stage, and transfer to a final recipient (col. 10, lines 31+). Particularly, the '075 patent teaches that the donor nucleus may contain one or more transgenes and that this genetic modification may take place prior to nuclear transfer and embryo reconstruction (col. 4, lines 4-8).

Accordingly, it would have been obvious to the skilled artisan, to modify the NT techniques taught by Campbell, to include serial nuclear transfer, wherein cells of the NT embryo are used for further rounds of NT, with a reasonable expectation of success. One of skill in the art would have been motivated to make this modification in view of the '075 patent's suggestion that serial nuclear transfer may provide for increased yields of viable embryos. Additionally, one of skill in the art would recognize that the '075 patent's teachings provide guidance to make genetic modifications prior to further rounds of NT. In particular, the '075 patent teaches that genetic modifications occur prior to NT and embryo reconstruction (col. 4, lines

4-8) and further, that NT embryos that are used in serial NT provide the donor nucleus. Thus, it would have been obvious for one of ordinary skill in the art to utilize the donor cell/nucleus, isolated from a NT embryo, and add further genetic modifications prior to another round of NT, with a reasonable expectation of success.

Thus, the claimed invention, as a whole, is clearly *prima facie* obvious in the absence of evidence to the contrary.

Claims 62, 134-143 are rejected under 35 U.S.C. 103(a) as being unpatentable over Campbell *et al.* (WO 97/07669, published 6 March 1997, Applicants' IDS) when taken with US Pat. No. 7,329,796 B2 (Campbell *et al.*, Published February 12, 2008).

Campbell is described above. They do not specifically teach using cells from the NT embryo/fetus or adult for further rounds of NT. However, prior to the time of filing of the claimed invention, the '796 patent teaches methods producing animal embryos by NT (Abstract). Particularly, they teach methods of preparing ungulate animals by forming a first embryo by NT, isolating cells from the first embryo and forming a second embryo by NT, transferring the second embryo to produce fetus that undergoes full fetal development to produce an ungulate animal (claim 1). Thus, the '796 patent provides guidance for serial nuclear transfer. The '796 patent teaches methods of producing transgenic animals that contain one or more transgenes, and that the genetic modification takes place prior to NT and embryo reconstruction (col. 3,, lines 55+). The '796 patent teaches that serial rounds of nuclear transfer may increase the yields of viable embryos (col. 8, lines 50+). The '796 document teaches using adult cells or fetal cells as donor cells (claims 7, 17, 19, 27, 28, 29).

Accordingly, it would have obvious to the skilled artisan, given the combined teachings of Campbell and the '796 patent, to modify the teachings of Campbell, and

utilize multiple rounds of NT, with a reasonable expectation of success. One of ordinary skill in the art, reading the '796 patent would recognize that the source of donor cell can be isolated from embryonic, fetal or adult tissue, and could be used from the animals produced by NT. Additionally, one of skill in the art the '796 patent's teachings provide guidance to make genetic modifications prior to further rounds of NT. In particular, the '075 patent teaches that genetic modifications occur prior to NT and embryo reconstruction (col. 3, lines 55+). Thus, given the combined teachings, it would have been obvious to the skilled artisan that 1) genetic modifications could be performed prior to a subsequent round of NT; and 2) that utilizing tissue from a cloned embryo/fetus or adult animal would provide an embryonic, fetal or adult donor cell for NT. These steps are all known and taught in the cited art. It is noted that KSR forecloses the argument that a specific teaching, suggestion, or motivation is required to support a finding of obviousness. See the recent Board decision *Ex parte Smith*, --USPQ2d--, slip op. at 20, (Bd. Pat. App. & Interf. June 25, 2007) (citing KSR, 82 USPQ2d at 1396) (available at **http://www.uspto.gov/web/offices/dcom/bpai/prec/fd071925.pdf**).

The combination of prior art cited above in all rejections under 35 U.S.C. 103 satisfies the factual inquiries as set forth in *Graham v. John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966). Once this has been accomplished the holdings in KSR can be applied (*KSR International Co. v. Teleflex Inc. (KSR)*, 550 USPQ2d 1385 (2007): "Exemplary rationales that may support a conclusion of obviousness include: (A) Combining prior art elements according to known methods to yield predictable results; (B) Simple substitution of one known element for another to obtain predictable results; (C) Use of known technique to improve similar devices (methods, or products) in the same way; (D) Applying a known technique to a known device (method, or product) ready for improvement to yield predictable results; (E) "Obvious to try" – choosing from a finite number of identified, predictable solutions, with a reasonable expectation of success; (F) Known work in

one field of endeavor may prompt variations of it for use in either the same field or a different one based on design incentives or other market forces if the variations are predictable to one of ordinary skill in the art; (G) Some teaching, suggestion, or motivation in the prior art that would have led one of ordinary skill to modify the prior art reference or to combine prior art reference teachings to arrive at the claimed invention."

In the instant case, at least rationale B), C) and D) apply to the instant invention. That is, one of skill in the art recognized that genetic modification must take place prior to nuclear transfer. Additionally, the art provides guidance to show that embryonic, fetal or adult donor cells may be for nuclear transfer to produce cloned animals. Thus, one of skill in the art could readily use cells produced by nuclear transfer, either from an embryo, fetus or adult cloned animal for subsequent genetic modifications and rounds of NT. Additionally, although not explicitly taught that the genetic modifications can occur either simultaneously, subsequently or sequentially, the combined art provides guidance to produce transgenic animals by NT that contain multiple genetic modifications. It would have been obvious to one of skill in the art to introduce transgenes into a donor cell by any of the claimed ways, because transfecting cells was a known technique recognized as part of the ordinary capabilities of one skilled in the art, and additionally, a finite number of identified solutions - either the addition of the transgenes simultaneously, sequentially or subsequently – would provide a reasonable expectation of success to producing a gene targeted donor cell with specific gene targeted modifications.

Thus, the claimed invention, as a whole, is clearly *prima facie* obvious in the absence of evidence to the contrary.

Claims 62, 144 and 146 are rejected under 35 U.S.C. 103(a) as being unpatentable over Campbell (WO 97/07669, published 6 March 1997, Applicants' IDS) when taken with Salminen *et al* (**Dev. Dynamics**, 212: 326-333, 1998).

Campbell is described above. However, they do not specifically teach that the modification of the nuclear genome places a transgene at a site which places the transgene under the control of an endogenous regulatory region (claim 144); and specifically that the endogenous regulatory region comprises a polyadenylation site.

However, prior to the time of filing, Salminen teach methods of producing a PolyA trap vector that is driven by a constitutive promoter that integrates with high frequency and traps genes with very different expression patters (Abstract).

Accordingly, in view of the combined teachings, it would have been obvious to modify the techniques taught by Campbell, and utilize a poly A trap vector, such as that taught by Salminen, with a reasonable expectation of success. One of ordinary skill in the art would have been motivated to make this modification in order to produce transgenic animals which could be used identify developmentally important genes, and study expression patterns of genes trapped *in vivo*.

Thus, the claimed invention, as a whole, is clearly *prima facie* obvious in the absence of evidence to the contrary.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Thaian N. Ton whose telephone number is (571)272-0736. The examiner can normally be reached on 9-5:30 M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Peter Paras can be reached on 571-272-4517. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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/Thaian N. Ton/
Primary Examiner, Art Unit 1632